

Biological Markers for Chemotherapy Induced toxicities in Patients with Malignancy

Thesis

*Submitted for the partial fulfillment of the M.D. degree in
Pediatrics*

Presented by

Rasha Adel Fathy Thabet

*M.B.B.Ch., M.Sc. pediatrics
Ain Shams University*

Under supervision of

Prof. Dr./ Galila Mohamed Mokhtar

*Professor of Pediatrics
Head of Pediatric Department and Hematolo-oncology Unit Faculty of
Medicine, Ain Shams University*

Prof. Dr. /Lobna Mohamed El Amin Shalaby

*Professor of Pediatric Oncology
Head of Pediatric Oncology Department of National Cancer Institute
Faculty of Medicine, Cairo University*

Prof. Dr./ Eman Mounir Sherif

*Professor of Pediatrics
Faculty of Medicine, Ain Shams University*

Prof. Dr. / Manal Mohamed Abd el Aziz

*Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University*

Dr. / Samar Mohamed Farid

*Ass. Professor of Pediatrics
Faculty of Medicine, Ain Shams University*

**Faculty of Medicine,
Ain Shams University
2014**



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وقل زدني علماً

صدق الله العظيم

سورة البقرة آية (32)



Acknowledgement

First, thanks are all to **ALLAH** the Most Merciful for supporting me all through my life.

I would like to express my deepest gratitude to **Prof. Dr. Galila Mohamed Mokhtar**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University. I feel highly honored by having the chance to work under her supervision. I had the privilege to benefit from her great knowledge.

I am also very grateful to **Prof. Dr. Lobna Mohamed El Amin Shalaby**, Professor of Pediatric Oncology Head of Pediatric Oncology Department of National Cancer Institute, Faculty of Medicine, Cairo University and, **Prof. Dr. Eman Mounir Sherif**, Professor of Pediatrics. Faculty of Medicine, Ain Shams University, for their close supervision, fruitful advices, and the great effort they have done throughout the whole work.

I would also like to thank **Prof. Dr. / Manal Mohamed Abd el Aziz**, Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University.

My deepest gratitude to **Dr. / Samar Mohamed Farid**, Ass. Professor of Pediatrics, Faculty of Medicine, Ain Shams University for her great effort with me throughout the whole study.



Rasha Adel Fathy Thabet

Contents

List of Abbreviations	i
List of Tables	v
List of Figures	vii
Review of literature	5
* Cancer Development.....	5
* Classification of cancer chemotherapy.....	44
* Chemotherapy induced toxicity.....	58
Subject and methods	80
Results	86
Discussion	125
Summary and conclusion	143
Recommendations	148
References	149
Arabic Summary	--

List of Abbreviations

5-FU	: 5 fluorouracil
ADE	: Cytarabine, daunorubicin, etoposide
ADRs	: Adverse Drug Reactions
AEL	: Acute erythroid leukemia
AIE	: Cytarabine, idarubicin, etoposide
ALCL	: Anaplastic large cell lymphoma
ALL	: Acute lymphocytic leukemia
allo-SCT	: Allogeneic stem cell transplantation
ALT	: Alanin aminotransferase
AMKL	: Acute megakaryocytic leukemia
AML	: Acute myelogenous leukemia
AMML	: Acute myelomonocytic leukemia
AMoL	: Acute monocytic leukemia
APL	: Acute promyelocytic leukemia
AST	: Aspartate aminotransferase
AVN	: Avascular necrosis
BFM	: Berlin-Frankfurt-Munster group
BMI	: Body mass index
BUN	: Blood Urea Nitrogen
CAD	: Coronary Artery Disease
CBC	: Complete Blood Count
CML	: Chronic myelogenous leukemia

List of Abbreviations (Cont.)

CNS	: Central Nervous System
CPM	: Cyclophosphamide
CRT	: Cranial radiotherapy
CT	: Computarized Tomography
DLBCL	: Diffuse large B-cell lymphoma
DNA	: Deoxiribonucleoprotein
EBV	: Epstein-Barr virus
ECHO	: Echocardiography
EFS	: Event-free survival
ER	: Endoplasmic reticulum
ESAs	: Erythropoiesis stimulating agents
FAB	: French-American-British
FISH	: Fluoresence in situ hybridization
GCSF	: Granulocyte colony stimulating factor
GFR	: Glomerular filtration rate
GH	: Growth Hormone
GI	: Gastrointestinal
GLP-2	: Glucagon-like peptide-2
GnRH	: Gonadotropin Releasing Hormone
GvHD	: Graft-versus-host disease
GvL	: Graft-versus-leukemia
HAM	: High-dose cytarabine and mitoxantrone

List of Abbreviations (Cont.)

Hb	:	Hemoglobin
HD ara-c	:	High-dose cytosine arabinoside
HF	:	Heart Failure
HRS	:	Hodgkin-Reed-Sternberg
HSCT	:	Hematopoietic stem cell transplants
IFN- α	:	Interferon α
IL-6	:	Interleukin 6
JMML	:	Juvenile myelomonocytic leukemia
LCLs	:	Large cell lymphomas
LVEF	:	Left Ventricular Ejection Fraction
MAbs	:	Monoclonal antibodies
MI	:	Myocardial infarction
MPO	:	Myeloperoxidase
MSC	:	Mesenchymal stem cells
MTX	:	Methotrexate
MVC	:	Micro vessel count
NB	:	Neuroblastoma
NCI	:	National Cancer Institute
NE	:	Neutrophil
NHL	:	Non Hogkin Lymphoma
NPY	:	Neuropeptides-Y
NRSTSs	:	Nonrhabdomyosarcoma soft tissue sarcomas

List of Abbreviations (Cont.)

OS	: Overall survival
PCR	: Polymerase chain reaction
PLT	: Platelet
Rb	: Retinoblastoma
RBS	: Random Blood Sugar
RNA	: Ribonucleoprotein
ROC	: Receiver-operating characteristic
RT	: Radiotherapy
SCT	: Stem cell transplantation
SMNs	: Second malignant neoplasms
SVC	: Superior vena cava
TG	: Triglyceride
TLC	: Total Leucocytic Count
TNF- α	: Tumor Necrotic Factor α
TnI	: Troponin I
TPO	: Thrombopoietin
VBL	: Vinblastine
VCR	: Vincristine
VEGF	: Vascular endothelial growth factor
VRL	: Vinorelbine
WBC	: White blood cell count

List of tables

<i>No.</i>	<i>Title</i>	<i>Page</i>
1	Signs and Symptoms of Childhood Cancers and Conditions That Can Mimic These Cancers	9
2	Correlation of histopathology, Immunophenotype, clinical features, cytogenetics and molecular features of childhood Non Hodgkin Lymphoma	25
3	Comparison between patients and control as regards socio-demographic data	87
4	Comparison between patients and controls as regards anthropometric data at presentation	87
5	Descriptive data of the patients as regards clinical data at presentation	88
6	Comparison of patients and controls as regard laboratory data on presentation	89
7	Comparison between anthropometric measurements of the patients at presentation, during the first and the second follow up	90
8	Comparison between laboratory variables of the patients at presentation, after first follow up and after second follow up	92
9	Correlation between dosage of chemotherapeutic agents and markers of organ toxicity during the first follow up	105
10	Linear regression model for prediction of cardiac troponin I level using the dose of doxorubicin administered	107
11	Correlation between the dosage of chemotherapeutic agents and biomarkers of organ toxicity during the second follow up.	109
12	Correlation between the dosage of chemotherapeutic agents and biomarkers of organ toxicity during the second follow up.	111

List of tables (Cont.)

<i>No.</i>	<i>Title</i>	<i>Page</i>
13	Linear regression model for prediction of GLP-2 level at the 2nd follow-up using the dose of methotrexate administered	114
14	Linear regression model for prediction of GLP-2 level at the 2nd follow-up using the dose of etoposide administered	116
15	Comparison between GLP-2 level in patients with and those without mucositis during first and second follow-up	117
16	Receiver-operating characteristic (ROC) curve analysis for prediction of the incidence of mucositis at the 1 st and 2 nd follow-up using GLP-2 level	118
17	Survival analysis among our patient during our follow up study	122

List of Figures

<i>No.</i>	<i>Title</i>	<i>Page</i>
1	Tumor angiogenesis	6
2	Gingival hyperplasia in a patient with monoblastic leukemia	20
3	Computed tomography scan in a patient with a large, left-sided axillary mass from which a biopsy was obtained. Biopsy findings were consistent with small noncleaved cell non-Hodgkin lymphoma	27
4	CT showing RT sided Wilms tumor	36
5	Gross nephrectomy specimen shows a Wilms tumor pushing the normal renal parenchyma to the side	37
6	CT scan of abdomen in a patient with a retroperitoneal mass arising from the upper pole of the left kidney and elevated urine catecholamines	39
7	Lateral plain radiograph of the knee reveals an osteosarcoma of the distal femur. The lesion is mainly posterior, with disruption and elevation of the periosteum (Codman triangle), and extends beyond the bone into the soft tissue.	41
8	Cell cycle	45
9	Ulcerative oral mucositis lesion on the buccal mucosa.	67
10	The patient shown in the previous image became short of breath after 5 cycles of chemotherapy. This chest radiograph was obtained before he was hospitalized. It shows scattered reticular opacities	71
11	Distribution of the studied patients	86

List of Figures (Cont.)

<i>No.</i>	<i>Title</i>	<i>Page</i>
12	Comparison between anthropometric measures of the studied patients at presentation, during the first follow up and during the second follow up.	91
13	Comparison between CBC finding in patients at baseline, during the first follow up and during the second follow up	93
14	Comparison between levels of ALT, AST and T. bilirubin at baseline, during the first and second follow up	94
15	Comparison between levels of creatinine, BUN and creat. clearance at baseline, after the first follow up and after the second follow up.	95
16	Comparison between the levels of RBS, TG and cholesterol at baseline, during the first follow up and during the second follow up.	96
17	Comparison between levels of cardiac troponin and GLP 2 at baseline, during the first follow up and during the second follow up	97
18	Changes in the level of ALT during follow up in different patients groups.	98
19	Changes in the level of BUN during follow up in different patients groups.	99
20	level of Cholesterol during follow up in different patients groups	100
21	GLP2 level changes in patients groups	101
22	Changes in RBS level in different patients groups	102
23	changes in triglyceride level in different patients groups	103
24	changes in cardiac troponin level in different patients groups	104

List of Figures (Cont.)

<i>No.</i>	<i>Title</i>	<i>Page</i>
25	Scatter plot with linear regression line for prediction of cardiac troponin I level using the dose of doxorubicin administered	107
26	Scatter diagram showing the correlation between dosage of doxorubicin and cardiac troponin	108
27	Scatter diagram showing the correlation between dosage of cyclophosphamide and ALT level	110
28	Scatter diagram showing the correlation between dosage of oral methotrexate and RBS level	112
29	Scatter diagram showing the correlation between dosage of IV methotrexate and GLP-2 level during the second follow up	113
30	Scatter plot with linear regression line for prediction of GLP-2 level using the dose of methotrxate administered.	114
31	Scatter diagram showing the correlation between dosage of IV Etoposide and GLP-2 level during the second	115
32	Scatter plot with linear regression line for prediction of GLP-2 level using the dose of etoposide administered	116
33	Receiver-operating characteristic (ROC) curve for prediction of the incidence of mucositis at the 1st follow-up using GLP-2 level	119
34	Receiver-operating characteristic (ROC) curve for prediction of the incidence of mucositis at the 1st follow-up using GLP-2 level	120
35	Kaplan-Meier survival curve for the whole study population.	123
36	Comparison between survival rate among patient with leukemia and those with lymphoma	124

Introduction

Chemotherapy is an important primary and adjuvant therapy for cancer patients. The cytotoxicity of antineoplastic agents affects not only tumor cells but also rapidly proliferating normal cells (**Hirotsani et al., 2006**).

Severe adverse drug reactions (ADRs) are a major issue for drug therapy because they can cause serious disorders and be life-threatening. Many severe ADRs appear to be idiosyncratic and unpredictable. Genetic factors may underlie susceptibility to severe ADRs, and identification of predisposing genotypes may improve drug therapy by facilitating prescreening of carriers for specific genetic biomarkers (**Tohkin et al., 2010**).

Advances in molecular biology and genetics over the past 60 years have facilitated development of multiple chemotherapeutic agents that are active against most common malignancies. However, significant heterogeneity in the efficacy and toxicity of these agents is consistently observed across human populations. (**Miller and Howard 2007**).

The spectrum of cardiac side-effects of cancer chemotherapy has expanded with the development of combination, adjuvant and targeted chemotherapies. Their

administration in multiple regimens has increased greatly. Cardiac toxicity of anthracyclines involves oxidative stress and apoptosis. High doses of the alkylating drugs cyclophosphamide and ifosfamide may result in a reversible heart failure and in life-threatening arrhythmias. Myocardial ischemia induced by the antimetabolites 5-fluorouracil and capecitabine impacts prognosis of patients with prior CAD. Severe arrhythmias may complicate administration of microtubule inhibitors (**Monsuez et al., 2010**).

Mesenchymal stem cells (MSC) are important cellular component of the bone marrow microenvironment in supporting hemopoiesis. MSCs are resistant to chemotherapy commonly used in hematologic malignancies but are relatively sensitive to anti-microtubule agents. However, the response of MSCs to other chemotherapeutic agents commonly used in solid tumour settings remains unknown (**Li et al., 2010**).

Common complications of chemotherapy thus include stomatitis and enterocolitis. Methotrexate (MTX) is an antimetabolite drug that blocks the production of biologically active forms of folic acid. The major lesions resulting from its cytotoxic effects occur in bone marrow and the intestinal tract (**Hirotsu et al., 2006**).